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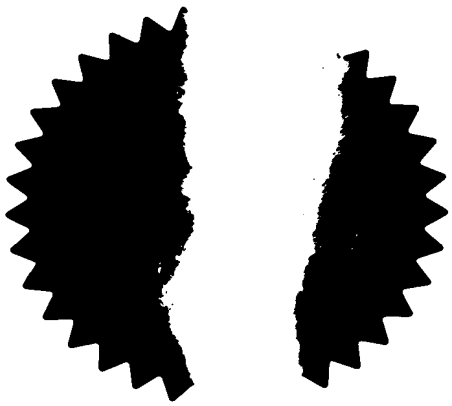

Signed Andrew Gerry

Dated 9 June 2003

EXPRESS MAIL NO.: EK651606192
DOCKET NO.: PC25373A

Patents Form 1/77

[redacted] Act 1977
(Rule 16)

01NOV02 E760124-1 001298
P01/7700 0.00-0225379.7

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

PC25373

2. Patent application number
(The Patent Office will fill in this part)

0225379.7

31 OCT 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number *(if you know it)*

689 267 3001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

THERAPEUTIC PROLINE DERIVATIVES

5. Name of your agent *(if you have one)*

Mr. P.G. Stuart

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)*

127001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	55
Claim *(s)*	2
Abstract	2
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature P.G. Stuart Date 31 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Mr. P.G. Stuart 01304.641367

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

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d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

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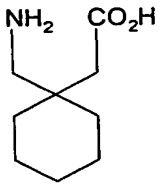
THERAPEUTIC PROLINE DERIVATIVES

FIELD OF THE INVENTION

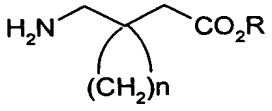
This invention relates to proline derivatives useful as pharmaceutical agents, to processes for their production, to pharmaceutical compositions containing them, and to their use for the treatment of the conditions set out below.

BACKGROUND TO THE INVENTION

Gabapentin (Neurontin®) is an anti-convulsant agent that is useful in the treatment of epilepsy and has recently been shown to be a potential treatment for neurogenic pain. It is 1-(aminomethyl)-cyclohexylacetic acid of structural formula:



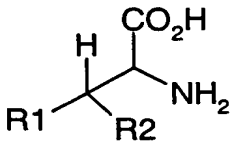
Gabapentin is one of a series of compounds of formula



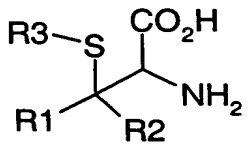
in which R is hydrogen or a lower alkyl radical and n is 4, 5, or 6. These compounds are described US-A-4024175 and its divisional US-A-4087544. Gabapentin is useful in the treatment of a number of diseases, including pain and epilepsy.

Gabapentin and related compounds, such as pregabalin, may be referred to as alpha-2-delta ligands. Alpha-2-delta ligands may be defined as compounds which selectively displace ^{3}H-gabapentin from porcine brain membranes indicating a high affinity interaction with the $\alpha_2\delta$ subunit of voltage-gated calcium channels. These types of compounds are also referred to as GABA analogs.

International Patent Applications No.s WO0230871 and WO0222568 describe compounds of the type I and type II, respectively,



I

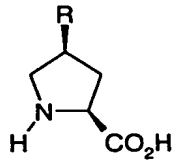


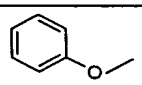
II

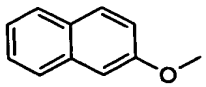
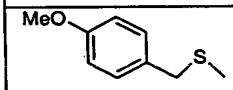
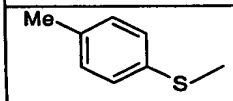
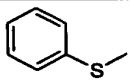
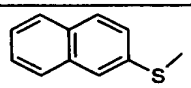
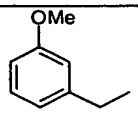
which also have affinity for the gabapentin binding site and have physiological activities similar to gabapentin, particularly with respect to analgesia.

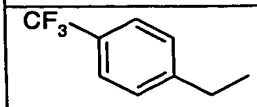
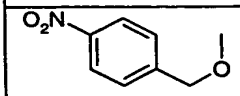
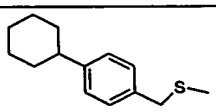
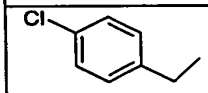
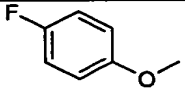
Certain of the compounds embraced within the broadest formula of the present invention have been disclosed for utilities not connected with the present invention, in particular according to Table 1:

Table 1



R	Ref
Bn0-(2S,4S)-4-(benzyloxy)pyrrolidine-2-carboxylic acid	Acta Chem Scand , 1990 , 243-51
BnS-(2S,4S)-4-(benzylthio)pyrrolidine-2-carboxylic acid	Chem Pharm Bull , 1972 , 543-49 J Med Chem , 1993 , 1902-13
	J.Med Chem , 1988 , 1148-60

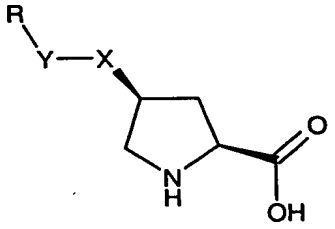
(2S,4S)-4-phenoxypyrrolidine-2-carboxylic acid	
 (2S,4S)-4-(2-naphthyloxy)pyrrolidine-2-carboxylic acid	J Med Chem , 1988 , 1148-60
 (2S,4S)-4-[(4-methoxybenzyl)thio]pyrrolidine-2-carboxylic acid	JOC, 1970, 1924-1927 J Med Chem , 1993 , 1902-1912
 (2S,4S)-4-[(4-methylphenyl)thio]pyrrolidine-2-carboxylic acid	J Med Chem , 1993 , 1402-13
 (2S,4S)-4-(phenylthio)pyrrolidine-2-carboxylic acid	J Med Chem , 1988 , 1148-60
 (2S,4S)-4-(2-naphthylthio)pyrrolidine-2-carboxylic acid	J Med Chem , 1988 , 1148-60
Bn- (2S,4S)-4-benzylpyrrolidine-2-carboxylic acid	J Med Chem , 1988 , 1148-60 JOC, 1995, 2925-30
	JOC, 1995, 2925-30

(2S,4S)-4-(3-methoxybenzyl)pyrrolidine-2-carboxylic acid	
 (2S,4S)-4-[4-(trifluoromethyl)benzyl]pyrrolidine-2-carboxylic acid	JOC, 1995, 2925-30
 (2S,4S)-4-[(4-nitrobenzyl)oxy]pyrrolidine-2-carboxylic acid	Japanese Patent Application No. JP 04154731
 (2S,4S)-4-[(4-cyclohexylbenzyl)thio]pyrrolidine-2-carboxylic acid	Japanese Patent Application No. JP 10265456
 (2S,4S)-4-(4-chlorobenzyl)pyrrolidine-2-carboxylic acid	UK Patent Application No. GB 2078733
 (2S,4S)-4-(4-fluorophenoxy)pyrrolidine-2-carboxylic acid	US Patent No. US 4311705

SUMMARY OF THE INVENTION

The present invention provides proline derivatives and their pharmaceutically acceptable salts, solvates and pro-drugs, useful in the treatment of a variety of disorders including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, and neuropathalogical disorders. The compounds provided may also be useful in the treatment of visceral pain, functional bowel disorders such as gastro-esophageal reflux, dyspepsia, irritable bowel syndrome and functional abdominal pain syndrome, and inflammatory bowel diseases such as Crohn's disease, ileitis, and ulcerative colitis, and other types of visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis. They may also be used for the treatment of premenstrual syndrome.

Thus, the present invention provides use of a compound of formula (I):



(I)

wherein

either X is O, S, NH or CH_2 and Y is CH_2 or a direct bond, or Y is O, S or NH and X is CH_2; and

R is a 3-12 membered cycloalkyl, 4-12 membered heterocycloalkyl, aryl or heteroaryl, where any ring may be optionally substituted with one or more substituents independently selected from

halogen, hydroxy, cyano, nitro, amino, hydroxycarbonyl,

C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl,

C_1-C_6 alkoxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, perfluoro C_1-C_6 alkyl, perfluoroC_1-C_6 alkoxy,

C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, di-C_1-C_6 alkylaminoC_1-C_6 alkyl,

C_1-C_6acyl, C_1-C_6acyloxy, C_1-C_6acyloxyC_1-C_6 alkyl, C_1-C_6 acylamino, C_1-C_6 alkylthio, C_1-C_6 alkylthiocarbonyl, C_1-C_6 alkylthioxo, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, aminosulfonyl, C_1-C_6 alkylaminosulfonyl, di-C_1-C_6 alkylaminosulfonyl, 3-8 membered cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and monocyclic heteroaryl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof, in medical therapy.

As a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the manufacture of a medicament for the treatment of a disorder for which the alpha-2-delta receptor is implicated. Suitably, a disorder for which the alpha-2-delta receptor is implicated is selected from epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, irritable bowel syndrome, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

As an alternative of the first further aspect of the present invention, there is provided a method of treatment of a mammal, including human, of a disorder for which the alpha-2-delta receptor is implicated, comprising effective administration of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

According to formula (I), suitably X is O, S or CH_2 and Y is CH_2 or a direct bond. Preferably, -Y-X- is a methylene, methyleneoxy, methylenethio, thio or oxy link. Particularly preferred, -Y-X- is an oxy link.

According to formula (I), R is suitably an optionally substituted aryl, heteroaryl or cyclohexyl, more suitably phenyl or isoquinolyl. R is suitably phenyl or isoquinolyl, optionally substituted with one or more substituents independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, perfluoro C_1-C_6 alkyl,

perfluoro C_1-C_6 alkoxy, cyano, amino C_1-C_6 alkyl, di-C_1-C_6 alkylaminoC_1-C_6 alkyl and monocyclic heteroaryl. R is preferably optionally substituted phenyl. Most preferably, R is phenyl, mono-substituted in the meta-position.

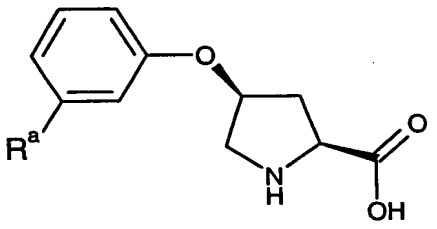
According to formula (I), a suitable optional substituent on R is halogen, preferably fluoro, chloro or bromo, most preferably chloro.

Particularly preferred compounds of the invention include those in which each variable in Formula (I) is selected from the suitable groups for each variable. Even more preferable compounds of the invention include those where each variable in Formula (I) is selected from the preferred or more preferred groups for each variable.

Preferred compounds of formula (I) are selected from:
(2*S*,4*S*)-4-(Benzylsulfanyl)-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-[(4-chlorobenzyl)oxy]-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-[(4-bromophenylthio]-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-phenylthio-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-[2-fluorophenoxy]-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-[(4-chlorophenoxy]-2-pyrrolidinecarboxylic acid;
(2*S*,4*S*)-4-[2-isoquinolinoxy]-2-pyrrolidinecarboxylic acid;
(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-2-carboxylic acid; and
(2*S*,4*S*)-4-(Benzyloxy)-2-pyrrolidinecarboxylic acid.

Certain compounds within the scope of formula (I) have been disclosed for non-therapeutic use. Thus, as a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, excluding any compound disclosed in the art for a non-therapeutic use, particularly those described in Table 1 above, i.e. (2S,4S)-4-(benzyloxy)pyrrolidine-2-carboxylic acid, (2S,4S)-4-(benzylthio)pyrrolidine-2-carboxylic acid, (2S,4S)-4-phenoxypyrrolidine-2-carboxylic acid, (2S,4S)-4-(2-naphthyloxy)pyrrolidine-2-carboxylic acid, (2S,4S)-4-[(4-methoxybenzyl)thio]pyrrolidine-2-carboxylic acid, (2S,4S)-4-[(4-methylphenyl)thio]pyrrolidine-2-carboxylic acid, (2S,4S)-4-(phenylthio)pyrrolidine-2-

carboxylic acid, (2S,4S)-4-(2-naphthylthio)pyrrolidine-2-carboxylic acid, (2S,4S)-4-benzylpyrrolidine-2-carboxylic acid, (2S,4S)-4-(3-methoxybenzyl)pyrrolidine-2-carboxylic acid, (2S,4S)-4-[4-(trifluoromethyl)benzyl]pyrrolidine-2-carboxylic acid, (2S,4S)-4-[(4-nitrobenzyl)oxy]pyrrolidine-2-carboxylic acid, (2S,4S)-4-[(4-cyclohexylbenzyl)thio]pyrrolidine-2-carboxylic acid, (2S,4S)-4-(4-chlorobenzyl)pyrrolidine-2-carboxylic acid and (2S,4S)-4-(4-fluorophenoxy)pyrrolidine-2-carboxylic acid. As an alternative aspect of the present invention, there is provided a compound of formula (Ia):



(Ia)

wherein R^a is selected from

halogen, hydroxy, cyano, nitro, amino, hydroxycarbonyl,

C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl,

C_1-C_6 alkoxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, perfluoro C_1-C_6 alkyl, perfluoroC_1-C_6 alkoxy,

C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, di-C_1-C_6 alkylaminoC_1-C_6 alkyl,

C_1-C_6acyl, C_1-C_6acyloxy, C_1-C_6acyloxyC_1-C_6 alkyl, C_1-C_6 acylamino,

C_1-C_6 alkylthio, C_1-C_6 alkylthiocarbonyl, C_1-C_6 alkylthioxo, C_1-C_6 alkoxycarbonyl,

C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino,

aminosulfonyl, C_1-C_6 alkylaminosulfonyl, di-C_1-C_6 alkylaminosulfonyl,

3-8 membered cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and monocyclic heteroaryl,

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Alkyl and alkoxy groups, containing the requisite number of carbon atoms, except where

indicated, can be unbranched- or branched-chain. Examples of alkyl include straight and branched chain groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include straight and branched chain groups such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Alkenyl and alkynyl groups as referred to herein include straight and branched ring aliphatic groups having one double or triple bond, respectively. Examples of alkenyl and alkynyl groups onclude ethenyl, prop-1-enyl, prop-2-enyl and ethynyl, prop-1-ynyl and prop-2-ynyl respectively.

4-8 membered heterocycloalkyl when used herein refers to a single ring system containing at least one ring heteroatom independently selected from O, S and N. 4-12 membered heterocycloalkyl when used herein refers to a single ring or fused ring system containing at least one ring heteroatom independently selected from O, S and N. Thus a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated or aromatic rings is within the definition of 4-12 membered heterocycloalkyl so long as the system also contains at least one fused ring which contains at least one of the aforementioned heteroatoms. Suitable heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc.

Heteroaryl when used herein refers to a single aromatic ring or fused aromatic ring system containing at least one ring heteroatom independently selected from O, S and N. Thus a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated or aromatic rings is within the definition of heteroaryl so long as the system also contains at least one fused aromatic ring which contains at least one of the aforementioned heteroatoms. Suitable heteroaryl groups include furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl,

1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazinyl, etc.

C_3-C_8 cycloalkyl as used herein refers to a single saturated or partially unsaturated carbocyclic ring system. C_3-C_{12} cycloalkyl as used herein refers to a single or fused carbocyclic ring system containing at least one saturated or partially unsaturated ring, where the other ring in a fused system may be phenyl. Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, indane and 1,2,3,4-tetrahydronaphthylene groups.

Aryl when used herein refers to phenyl or naphthyl.

Acyl as used herein refers to aliphatic or cyclic hydrocarbons attached to a carbonyl group through which the substituent bonds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, which may contain isotopic substitutions (e.g. D_2O, d6-acetone, d6-DMSO), are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

Although the stereochemistry on the pyrrolidine ring of formula (I) is fixed, certain of the compounds of the present invention may possess one or more further chiral centers and each center may exist in the R(D) or S(L) configuration. The present

invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the invention or a suitable salt or derivative thereof. An individual enantiomer of a compound of the invention may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

The present invention also includes all suitable isotopic variations of a compound of the invention or a pharmaceutically acceptable salt thereof. An isotopic variation of a compound of the invention, or a pharmaceutically acceptable salt thereof, is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention, and pharmaceutically acceptable salts thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the compounds of the invention and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

The compounds of the present invention are amino acids. Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate non-toxic inorganic or organic acids or bases. Suitable acid addition salts are the hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, fumarate, aspartate, besylate, bicarbonate/carbonate, camsylate, D and L-lactate, D and L-tartrate, edisylate, mesylate, malonate, orotate, gluceptate, methylsulphate, stearate, glucuronate, 2-napsylate, tosylate, hibenzate, nicotinate, isethionate, malate, maleate, citrate, gluconate, succinate, saccharate, benzoate, esylate, and pamoate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc, choline, diolamine, olamine, arginine, glycine, tromethamine, benzathine, lysine, meglumine and diethylamine salts. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The compounds of the invention may also be formed as a zwitterion.

A suitable salt for amino acid compounds of the present invention is the hydrochloride salt. For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

Also included within the present scope of the compounds of the invention are polymorphs thereof.

Pro-drugs of the above compounds of the invention are included in the scope of the instant invention. The effectiveness of an orally administered drug is dependent upon the drug's efficient transport across the mucosal epithelium and its stability in entero-hepactic circulation. Drugs that are effective after parenteral administration but less effective orally, or whose plasma half-life is considered too short, may be chemically modified into a pro-drug form. A pro-drug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other in vivo processes to the parent bioactive form. The chemically modified drug, or pro-drug, should have a different pharmacokinetic profile to the parent, enabling easier absorption across the

mucosal epithelium, better salt formulation and/or solubility, improved systemic stability (for an increase in plasma half-life, for example). These chemical modifications may be:-

(1) Ester or amide derivatives which may be cleaved by, for example, esterases or lipases. For ester derivatives, the ester is derived from the carboxylic acid moiety of the drug molecule by known means. For amide derivatives, the amide may be derived from the carboxylic acid moiety or the amine moiety of the drug molecule by known means.

(2) Peptides which may be recognized by specific or nonspecific proteinases. A peptide may be coupled to the drug molecule via amide bond formation with the amine or carboxylic acid moiety of the drug molecule by known means.

(3) Derivatives that accumulate at a site of action through membrane selection of a pro-drug form or modified pro-drug form.

(4) Any combination of 1 to 3.

It will be further appreciated by those skilled in the art that certain moieties known to those skilled in the art as "pro-moieties," for example as described in "Design of Pro-drugs" by H. Bundgaard (Elsevier) 1985, may be placed on appropriate functionalities when such functionalities are present in compounds of the invention also to form a "pro-drug." Further, certain compounds of the invention may act as pro-drugs of other compounds of the invention. All protected derivatives, and pro-drugs, of the compounds of the invention are included within the scope of the invention.

Research has shown that the oral absorption of certain drugs may be increased by the preparation of "soft" quaternary salts. The quaternary salt is termed a "soft" quaternary salt since, unlike normal quaternary salts, e.g., $R\text{-}N^{+}(CH_3)_3$, it can release the active drug on hydrolysis. "Soft" quaternary salts have useful physical properties compared with the basic drug or its salts. Water solubility may be increased compared with other salts, such as the hydrochloride, but more important there may be an increased absorption of the drug from the intestine. Increased absorption is probably due to the fact that the "soft" quaternary salt has surfactant properties and is capable of forming micelles and unionized ion pairs with bile acids, etc., which are able to

penetrate the intestinal epithelium more effectively. The pro-drug, after absorption, is rapidly hydrolyzed with release of the active parent drug.

Aminoacyl-glycolic and -lactic esters are known as pro-drugs of amino acids (Wermuth C.G., *Chemistry and Industry*, 1980:433-435). The carbonyl group of the amino acids can be esterified by known means. Pro-drugs and soft drugs are known in the art (Palomino E., *Drugs of the Future*, 1990;15(4):361-368). The last two citations are hereby incorporated by reference.

The invention also relates to therapeutic use of the present compounds as agents for treating or relieving the symptoms of neurodegenerative disorders. Such neurodegenerative disorders include, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia. Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular accident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. These vascular disorders may occur in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like. Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia. The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the present invention are useful for the general treatment of pain, particularly neuropathic pain. Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is exclusively activated by noxious stimuli via peripheral transducing mechanisms (Millan 1999 Prog. Neurobio. 57: 1-164 for an integrative Review). These sensory fibres are known as nociceptors and are characterised by small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred after complex processing in the dorsal horn, either directly or via brain stem relay nuclei to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Intense acute pain and chronic pain may involve the same pathways driven by pathophysiological processes and as such cease to provide a protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states. Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered. There is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. This leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain these mechanisms can be useful and allow for the repair processes to take place and the hypersensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury. This injury often leads to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning, or stabbing; 2)

pain responses to noxious stimuli are exaggerated (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Although patients with back pain, arthritis pain, CNS trauma, or neuropathic pain may have similar symptoms, the underlying mechanisms are different and, therefore, may require different treatment strategies. Therefore pain can be divided into a number of different areas because of differing pathophysiology, these include nociceptive, inflammatory, neuropathic pain etc. It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. Back pain, Cancer pain have both nociceptive and neuropathic components.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and sensitise the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994 Textbook of Pain 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmitted rapidly and are responsible for the sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey the dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to pain from strains/sprains, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, burns, myocardial infarction, acute pancreatitis, and renal colic. Also cancer related acute pain syndromes commonly due to therapeutic interactions such as chemotherapy toxicity, immunotherapy, hormonal therapy and radiotherapy. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to, cancer pain which may be tumour related pain, (e.g. bone pain, headache and facial pain, viscera pain) or associated with cancer therapy (e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes), back pain which may be due to herniated or ruptured intervertabral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (IASP definition). Nerve damage can be caused by

trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include but are not limited to, Diabetic neuropathy, Post herpetic neuralgia, Back pain, Cancer neuropathy, HIV neuropathy, Phantom limb pain, Carpal Tunnel Syndrome, chronic alcoholism, hypothyroidism, trigeminal neuralgia, uremia, or vitamin deficiencies. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patients quality of life (Woolf and Mannion 1999 Lancet 353: 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd 1999 Pain Supp. 6: S141-S147; Woolf and Mannion 1999 Lancet 353: 1959-1964). They include spontaneous pain, which can be continuous, or paroxysmal and abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events activated in response to tissue injury or the presence of foreign substances, which result in swelling and pain (Levine and Taiwo 1994: Textbook of Pain 45-56). Arthritic pain makes up the majority of the inflammatory pain population. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of RA is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson 1994 Textbook of Pain 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder 2002 Ann Pharmacother. 36: 679-686; McCarthy et al., 1994 Textbook of Pain 387-395). Most patients with OA seek medical attention because of pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Other types of inflammatory pain include but are not limited to inflammatory bowel diseases (IBD),

Other types of pain include but are not limited to;

- Musculo-skeletal disorders including but not limited to myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis, polymyositis, pyomyositis.

- Central pain or 'thalamic pain' as defined by pain caused by lesion or dysfunction of the nervous system including but not limited to central post-stroke pain, multiple sclerosis, spinal cord injury, Parkinson's disease and epilepsy.

- Heart and vascular pain including but not limited to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma, scleredoma, skeletal muscle ischemia.

- Visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and – for IBD, Crohn's disease, ileitis, and ulcerative colitis, which all regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

- Head pain including but not limited to migraine, migraine with aura, migraine without aura cluster headache, tension-type headache.

- Orofacial pain including but not limited to dental pain, temporomandibular myofascial pain.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

The biological activity of the alpha-2-delta ligands of the invention may be measured in a radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue (Gee N.S., Brown J.P., Dissanayake V.U.K., Offord J., Thurlow R., Woodruff G.N., *J. Biol. Chem.*, 1996;271:5879-5776). Results may be expressed in terms of μM or nM α2δ binding affinity.

The compounds of the invention may also be administered in combination, separately, simultaneously or sequentially, with one or more other pharmacologically active agents. Suitable agents, particularly for the treatment of pain, include:

(i) opioid analgesics, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;

(ii) nonsteroidal antiinflammatory drugs (NSAIDs), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen,ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone,

naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and their pharmaceutically acceptable salts;

(iii) barbiturate sedatives, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts;

(iv) benzodiazepines having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts,

(v) H_1 antagonists having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their pharmaceutically acceptable salts;

(vi) miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts;

(vii) skeletal muscle relaxants, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, orphrenadine and their pharmaceutically acceptable salts,

(viii) NMDA receptor antagonists, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid and their pharmaceutically acceptable salts;

(ix) alpha-adrenergic active compounds, e.g. doxazosin, tamsulosin, clonidine and 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

(x) tricyclic antidepressants, e.g. desipramine, imipramine, amytriptiline and nortriptiline;

(xi) anticonvulsants, e.g. carbamazepine and valproate;

(xii) serotonin reuptake inhibitors, e.g. fluoxetine, paroxetine, citalopram and sertraline;

(xiii) mixed serotonin-noradrenaline reuptake inhibitors, e.g. milnacipran, venlafaxine and duloxetine;

(xiv) noradrenaline reuptake inhibitors , e.g. reboxetine;

(xv) Tachykinin (NK) antagonists, particularly Nk-3, NK-2 and NK-1 e.g.

antagonists, (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S)

(xvi) Muscarinic antagonists, e.g oxybutin, tolterodine, propiverine, tropsium chloride and darifenacin;

(xvii) COX-2 inhibitors, e.g. celecoxib, rofecoxib and valdecoxib;

(xviii) Non-selective COX inhibitors (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);

(xix) coal-tar analgesics, in particular, paracetamol;

(xx) neuroleptics, such as droperidol;

(xxi) Vanilloid receptor agonists, e.g. resinferatoxin;

(xxii) Beta-adrenergic compounds such as propranolol;

(xxiii) Local anaesthetics, such as mexiletine;

(xxiv) Corticosteriods, such as dexamethasone

(xxv) serotonin receptor agonists and antagonists;

(xxvi) cholinergic (nicotinic) analgesics; and

(xxvii) miscellaneous agents such as Tramadol®.

Thus, the invention further provides a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or pro-drug thereof, and a compound or class of compounds selected from the group (i)-(xxvii), above. There is also provided a pharmaceutical composition composition comprising such a combination, together with a pharmaceutically acceptable excipient, diluent or carrier, particularly for the treatment of a disease for which an alpha-2-delta ligand is implicated.

Combinations of the compounds of the present invention and other therapeutic agents may be administered separately, sequentially or simultaneously. Thus, the present invention extends to a kit comprising a compound of formula (I), one or more other therapeutic agents, such as those listed above, and a suitable container.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or pro-drug thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

The compounds of the invention can be administered alone but will generally be administered in an admixture with suitable pharmaceutical excipient(s), diluent(s) or carrier(s) selected with regard to the intended route of administration and standard pharmaceutical practice. If appropriate, auxiliaries can be added. Auxiliaries are preservatives, anti-oxidants, flavours or colourants. The compounds of the invention may be of immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release type.

The compounds of the present invention can be administered, for example but not limited to, the following route: orally, buccally or sublingually in the form of tablets, capsules, multi-and nano-particulates, gels, films (incl. muco-adhesive), powder, ovules, elixirs, lozenges (incl. liquid-filled), chews, solutions, suspensions and sprays. The compounds of the invention may also be administered as osmotic dosage form, or in the form of a high energy dispersion or as coated particles or fast-dissolving, fast - disintegrating dosage form as described in Ashley Publications, 2001 by Liang and Chen. The compounds of the invention may be administered as crystalline or amorphous products, freeze dried or spray dried. Suitable formulations of the compounds of the invention may be in hydrophilic or hydrophobic matrix, ion-exchange resin complex, coated or uncoated form and other types as described in US 6,106,864 as desired. Such pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), mannitol, disintegrants such as sodium starch glycolate, crosscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), triglycerides, hydroxypropylcellulose (HPC), bentonite sucrose, sorbitol, gelatin and acacia. Additionally, lubricating agents may be added to solid compositions such as magnesium

stearate, stearic acid, glyceryl behenate, PEG and talc or wetting agents, such as sodium lauryl sulphate. Additionally, polymers such as carbohydrates, phospoholipids and proteins may be included.

Fast dispersing or dissolving dosage fromulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol or xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used, i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

The solid dosage form, such as tablets are manufactured by a standard process, for example, direct compression or a wet, dry or melt granulation, melt congealing and extrusion process. The tablet cores which may be mono or multi-layer may be coated with appropriate overcoats known in the art.

Solid compositions of a similar type may also be employed as fillers in capsules such as gelatin, starch or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. Liquid compositions may be employed as fillers in soft or hard capsules such as gelatin capsule. For aqueous and oily suspensions, solutions, syrups and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol, methylcellulose, alginic acid or sodium alginate, glycerin, oils, hydrocolloid agents and combinations thereof. Moreover, formulations containing these compounds and excipients may be presented as a dry product for constitution with water or other suitable vehicles before use.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

The compounds of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, intraduodenally, or intraperitoneally, intraarterially, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intraspinally or subcutaneously, or they may be administered by infusion, needle-free injectors or implant injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution, suspension or emulsion (or system so that can include micelles) which may contain other substances known in the art, for example, enough salts or carbohydrates such as glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. For some forms of parenteral administration they may be used in the form of a sterile non-aqueous system such as fixed oils, including mono- or diglycerides, and fatty acids, including oleic acid. The preparation of suitable parenteral formulations under sterile conditions for example lyophilisation is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g. sterile, pyrogen-free water) before use.

Also, the compounds of the present invention can be administered intranasally or by inhalation. They are conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser (preferably an atomiser using

electrohydrodynamics to produce a fine mist) or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubron (trade mark) or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol (optionally, aqueous ethanol) or a suitable agent for dispersing, solubilising or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry powder formulation or suspension formulation for inhalation the compounds of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling, use of supercritical fluid crystallisation or by spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1□g to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100□l. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents may be used in place of propylene glycol, for example glycerol or polyethylene glycol.

Alternatively, the compounds of the invention may be administered topically to the skin, mucosa, dermally or transdermally, for example, in the form of a gel, hydrogel, lotion, solution, cream, ointment, dusting powder, dressing, foam, film, skin patch,

wafers, implant, sponges, fibres, bandage, microemulsions and combinations thereof. For such applications, the compounds of the invention can be suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, water, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, alcohols such as ethanol. Alternatively, penetration enhancers may be used. The following may also be used polymers, carbohydrates, proteins, phospolipids in the form of nanoparticles (such as niosomes or liposomes) or suspended or dissolved. In addition, they may be delivered using iontophoresis, electroporation, phonophoresis and sonophoresis.

Alternatively, the compounds of the invention can be administered rectally, for example in the form of a suppository or pessary. They may also be administered by vaginal route. For example, these compositions may be prepared by mixing the drug with a suitable non-irritant excipient(s), such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the cavity to release the drug.

The compounds of the invention may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline. A polymer may be added such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer (e.g. hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), or a heteropolysaccharide polymer (e.g. gelan gum). Alternatively, they may be formulated in an ointment such as petrolatum or mineral oil, incorporated into bio-degradable (e.g. absorbable gel sponges, collagen) or non-biodegradable (e.g. silicone) implants, wafers, drops, lenses or delivered via particulate or vesicular systems such as niosomes or liposomes. Formulations may be optionally combined with a preservative, such as benzalkonium chloride. In addition, they may be delivered using iontophoresis.

They may also be administered in the ear, using for example but not limited to the drops.

The compounds of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, taste-masking, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

The term 'administered' includes delivery by viral or non-viral techniques. Viral delivery mechanisms include but are not limited to adenoviral vectors, adeno-associated viral (AAV) vectors, herpes viral vectors, retroviral vectors, lentiviral vectors, and baculoviral vectors. Non-viral delivery mechanisms include lipid mediated transfection, lipsomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

Thus, as a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) and a suitable excipient, diluent or carrier.

The element of the pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate

number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active components. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compounds being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compounds. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

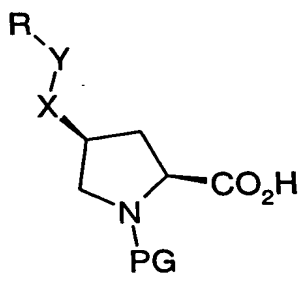
The pharmaceutical composition according to the present invention can, if desired, also contain one of more compatible therapeutic agents. In particular, the composition can be combined with any one or more compounds useful in the treatment of pain, such as those listed above. Thus, the present invention presents a pharmaceutical composition comprising a compound of formula (I), one or more other pharmacologically active agents and one or more pharmaceutically acceptable carriers.

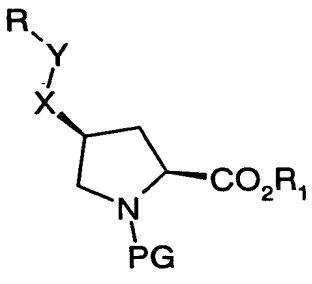
It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

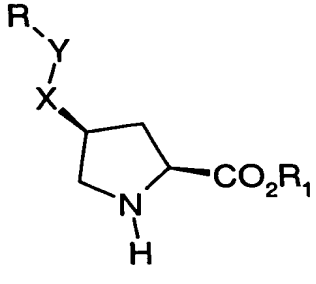
GENERAL METHODS

The compounds of formula (I) can be synthesised using the various methods set out below:

According to the first process, (A), a compound of formula (I) may be prepared by deprotection of a compound of formula (II), (III) or (IV)

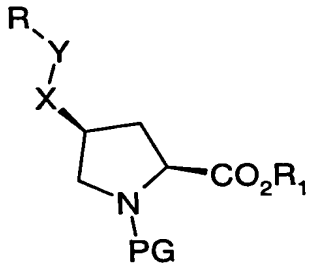

(II)


(III)


(IV)

where R, X and Y are as described for formula (I), R_1 is a suitable carboxylic acid protecting group, such as C_{1-6} alkyl, and PG is a suitable protecting group such as tert-butoxycarbonyl, by conventional methods, e.g. acid mediated hydrolysis using a strong acid, such as trifluoroacetic acid or hydrochloric acid, in a suitable solvent, such as dioxan or dichloromethane.

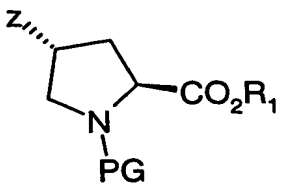
Compounds of formula (II) may be prepared by hydrolysis of the ester functionality of compound (V),


(V)

where X, Y, R and R_1 are as defined above and hydrolysis is facilitated by an alkali metal hydroxide, such as lithium hydroxide, in a suitable solvent, such as aqueous dioxan.

Compounds of formula (V) can be formed by the following methods:

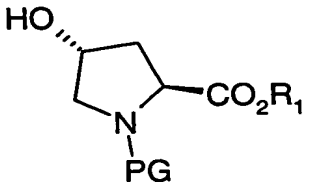
i) Reaction of a compound of formula (VI)



(VI)

where Z is a suitable leaving group, such as mesylate, tosylate, triflate or halo, with a compound RYX-H, using a suitable base, such as an alkali metal salt, such as K_2CO_3 or an alkali metal hydride, such as NaH, in a suitable solvent, such as DMF, at a temperature of 20-140°C.

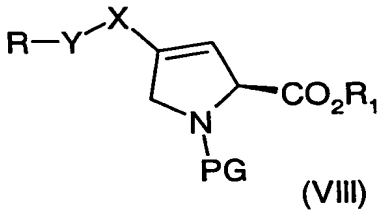
ii) Where RYX- is ArO-, where Ar is an optionally substituted aryl or heteroaryl ring, reaction of a compound of formula (VII)



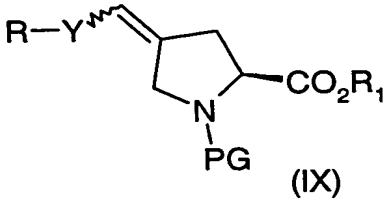
(VII)

with a compound of formula ArOH, using Mitsunobu conditions of a suitable azidodicarboxylate, such as DIAD and triphenylphosphine or tributylphosphine in a suitable solvent, such as THF, at a temperature of 25-60°C.

iii) Hydrogenolysis of a compound of formula (VIII) or, where X is CH_2, (IX).



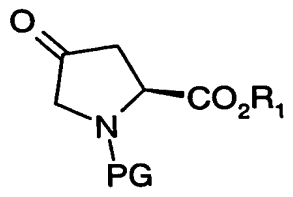
(VIII)



(IX)

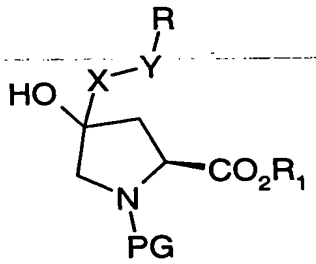
with a suitable catalyst such as palladium on carbon.

Compounds of formula (IX) can be prepared by reaction of compounds of formula (X) using Wittig chemistry with a suitable phosphorane or phosphate.



(X)

Compounds of formula (VIII) and (IX) can also be prepared by dehydration of compounds of the formula (XI) by acid catalysed dehydration.



(XI)

Compounds of the formula IX can be prepared by addition of an organometallic to compounds of the formula VIII, e.g., addition of benzylmagnesium bromide to VIII in a suitable solvent, such as THF, at a temperature of –78°C – 20°C

Referring to the general methods above, it will be readily understood to the skilled person that where protecting groups are present, these will be generally interchangeable with other protecting groups of a similar nature, e.g. where an amine is described as being protected with a *tert*-butoxycarbonyl group, this may be readily interchanged with any suitable amine protecting group.

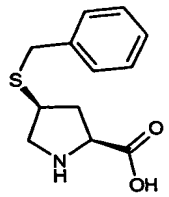
The present invention is illustrated by the following non-limiting examples and intermediates, where the following abbreviations are used:

THF	Tetrahydrofuran
DMF	Dimethylformamide
DIAD	Diisopropyl azodicarboxylate
EtOAc	Ethyl acetate
DCM	Dichloromethane
rt	Room temperature
MeOH	Methanol
EtOH	Ethanol
TFA	Trifluoroacetic acid

BOC tert butyloxycarbonyl

EXAMPLE 1

(2*S*,4*S*)-4-(Benzylsulfanyl)-2-pyrrolidinecarboxylic acid



To a solution of (2S, 4S)-4-Benzylsulfanyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (Preparation 2, 130mg, 3.3mmol) in dichloromethane (2.5ml) was added trifluoroacetic acid (2.5ml) and the mixture stirred at room temperature under a nitrogen atmosphere for 36 hours. The solvent was removed under reduced pressure and the residue purified by ion-exchange chromatography using Dowex™ 50WX8-200 resin eluting first with water and then with 10% aq ammonia to give the title compound (66mg, 75%) as a white solid.

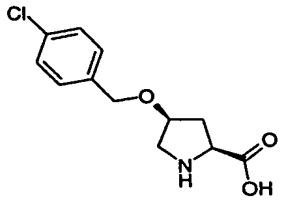
^{1}H-NMR (400MHz, D_2O) δ = 1.88-1.98 (1H, m); 2.45-2.56 (1H, m); 3.07-3.13 (1H, m); 3.22-3.38 (2H, m); 3.66-3.74 (2H, s); 3.93-4.01 (1H, m); 7.11-7.29 (5H, m)

LRMS (electrospray) : m/z [MH^+] 238; [MNa+] 260; [MH^-] 236

Microanalysis : Found C, 59.36; H, 6.33; N, 5.77. $C_{12}H_{15}NO_2S$. 0.3 H_2O requires C, 59.38; H, 6.48; N, 5.77

Example 2

(2*S*,4*S*)-4-[(4-chlorobenzyl)oxy]-2-pyrrolidinecarboxylic acid



(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-[(4-chlorobenzyl)oxy]-2-pyrrolidinecarboxylic acid (Preparation 4, 96mg, 0.38mmol) was dissolved in dichloromethane (5ml). Trifluoroacetic acid (5ml) was added and the mixture left overnight at room temperature. The reaction mixture was partitioned between dichloromethane (25ml) and water (25ml). The aqueous layer was separated, washed with more dichloromethane (25ml)

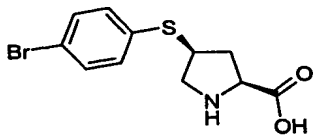
and evaporated to dryness. The product was purified using Dowex™ 50WX8-200 resin, eluting first with water then 9:1 water:ammonia yielding the title compound (5mg, 5% yield) as a white solid.

^{1}H-NMR (400MHz, CD_3OD) δ = 2.4-2.5(m, 1H), 2.6-2.7(m, 1H), 3.4-3.5(m, 1H), 3.6-3.7(m, 1H), 4.5-4.7(m, 4H), 7.3-7.5(m, 4H).

LCMS (electrospray): m/z [M^-] 254

Example 3

(2*S*,4*S*)-4-[(4-bromophenylthio]-2-pyrrolidinecarboxylic acid



(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (Preparation 7, 54mg, 0.14mmol) was dissolved in 4M HCl in dioxan and stirred for 2h at rt. The solvent was removed in vacuo to give a cream solid (32mg, 76%).

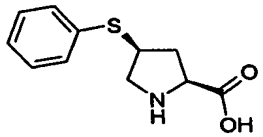
^{1}H-NMR (400MHz, CD_3OD) δ = 2.20 (1H, m), 2.83 (1H, m), 3.32 (1H, m), 3.70 (1H, m), 4.15 (1H, m), 4.50 (1H, m), 7.40 (2H, d), 7.55 (2H, m).

LRMS (electrospray) : m/z [MH^+] 302, 304.

Microanalysis : Found C, 39.01; H, 4.23; N, 4.14. $C_{11}H_{12}NO_2SBr$. 0.9 HCl requires C, 39.44; H, 3.88; N, 4.18.

Example 4

(2*S*,4*S*)-4-phenylthio-2-pyrrolidinecarboxylic acid



The title compound was made by the method of Example 3 starting from the title compound of Preparation 8. The yield was 60% and the title compound was a white solid.

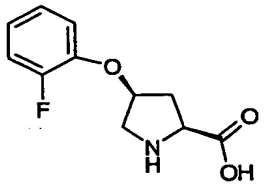
^{1}H-NMR (400MHz, CD_3OD) δ = 2.19 (1H, m), 2.80 (1H, m), 3.34 (1H, m), 3.70 (1H, m), 4.10 (1H, m), 4.56 (1H, m), 7.030-7.60 (5H, m).

LCMS (Electrospray): m/z [MH^+] 224.

Microanalysis : Found C, 48.95; H, 5.50; N, 4.97. $C_{11}H_{13}NO_2S$. HCl. $0.5H_2O$ requires C, 49.16; H, 5.63; N, 5.21.

Example 5

(2*S*,4*S*)-4-[2-fluorophenoxy]-2-pyrrolidinecarboxylic acid



The title compound was made by the method of Example 3 in 74% yield starting from the title compound from preparation 10.

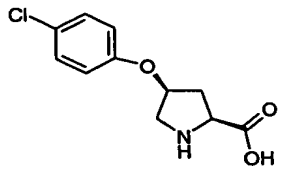
^{1}H-NMR (400MHz, MeOD): δ= 2.60 – 2.76 (m, 2H), 3.57 – 3.65 (m, 1H), 3.75 (d, 2H), 4.56 – 4.64 (m, 1H), 4.85 (s, 3H), 5.18 – 5.24 (m, 1H), 6.98 – 7.19 (m, 4H).

LRMS (electrospray): [M-1] 224, [MH^+] 226.

Microanalysis: Found: C, 50.38; H, 4.95; N, 5.29% $C_{11}H_{12}FNO_3$ requires C,50.49; H, 5.01, N, 5.35%

Example 6

(2*S*,4*S*)-4-[(4-chlorophenoxy]-2-pyrrolidinecarboxylic acid



The BOC protected product (250mg, 0.73mmol) from Preparation 12 was stirred in 4M HCl in dioxan (5ml) at 0° C for 2 hours. Diethylether (10ml) was added and the resultant precipitate filtered off and washed with diethylether to give the title compound (178mg, 87%).

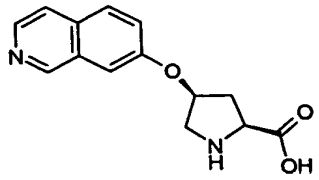
^{1}H-NMR (400 MHz, MeOD): δ =2.59 –2.71 (m, 2H), 3.56 – 3.72 (m, 2H), 4.57 – 4.66(m, 1H) , 4.82 – 4.93 (M, 3H), 5.17 – 5.25 (m, 1H), 6.88 – 6.98 (m, 2H), 7.26 – 7.36 (m, 2H).

LRMS (Electrospray): [M-1] 240, [MH^+] 242, [MNa^+] 264.

Microanalysis: Found: C, 47.48; H, 4.71; N, 4.92. $C_{11}H_{12}ClNO_3.HCl$ requires C, 47.50; H, 4.71; N, 5.04%

Example 7

(2*S*,4*S*)-4-[2-isoquinolinoxy]-2-pyrrolidinecarboxylic acid



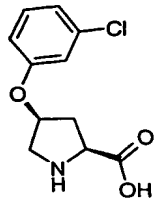
(2S, 4S)-4-(Isoquinolin-7-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butylester (Preparation 13, 120mg, 0.29mmol) was stirred in TFA (3ml) for 4.5 hours at room temperature. The solvent was removed in vacuo and triturated with diethyl ether to give an extremely hygroscopic solid which was redissolved in 2N HCl (3ml) and stirred at room temperature for one hour. The solution was washed once with diethylether (5ml) and the aqueous evaporated to give a foam. Tritruation with ether gave the title compound as a glass (24mg, 28%).

^{1}H-NMR (400 MHz, CH_3OD): δ = 2.68-2.80(m, 1H), 2.82 – 2.97 (m, 1H), 3.75 – 3.91 (m, 2H), 4.62 – 4.75 (m, 1H), 4.75 – 4.96 (m, 5H exchangeable), 5.48 – 5.60 (m, 1H), 7.75 – 7.81 (m, 1H), 7.98 – 8.02 (m, 1H), 8.26 (d, 1H), 8.39 – 8.55 (m, 2H), 9.64 (s, 1H)

LRMS (Electrospray) [M-1] 257, [MH^+] 259

Example 8

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-2-carboxylic acid



The title compound was made by the method of Example 6; washing the product with diethyl ether (2x20ml), to yield a white solid (52mg, 93%).

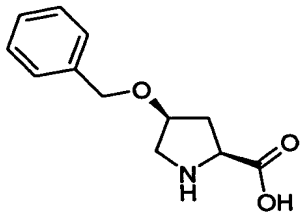
^{1}H NMR (400 MHz, CD_3OD): δ = 2.65 (m, 2H), 3.60 (dd, 1H), 3.70 (d, 1H), 4.60 (dd, 1H), 5.02 (m, 1H), 6.88 (m, 1H), 6.97 (s, 1H), 7.03 (d, 1H), 7.29 (dd, 1H).

LRMS (Electrospray [MH^+] 242, [M-1] 240.

Microanalysis: Found, C, 46.97; H, 4.70; N, 4.90. $C_{11}H_{12}ClNO_3.HCl.0.1H_2O$ requires C, 47.20; H, 4.75; N, 5.00.

Example 9

(2*S*,4*S*)-4-(Benzyloxy)-2-pyrrolidinecarboxylic acid



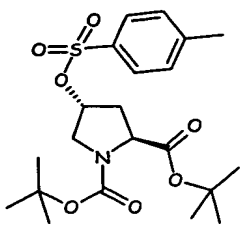
(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(benzyloxy)-2-pyrrolidinecarboxylic acid (Preparation 17, 150mg, 0.47mmol) was dissolved in dichloromethane (5ml). Trifluoroacetic acid (5ml) was added and the mixture left stirring overnight at room temperature. The reaction mixture was partitioned between dichloromethane (25ml) and water (25ml). The aqueous layer was separated, washed with more dichloromethane (25ml) and evaporated to dryness. The product was purified using an ion exchange column (Dowex 50WX8-200 resin), eluting first with water then 9:1 water:ammonia yielding the title compound (34mg, 33% yield) as a white solid.

^{1}H-NMR (400MHz, CD_3OD) δ = 2.3-2.5 (m, 1H), 3.1-3.18 (m, 1H), 3.4-3.5 (d, 1H), 3.9-3.95(m, 1H), 4.2 (s, 1H), 4.4-4.55 (dd, 3H), 7.2-7.4 (m, 5H).

LCMS (Electrospray): m/z [MNa^+] 244.

Preparation 1

(2S, 4R)-4-(Toluene-4-sulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



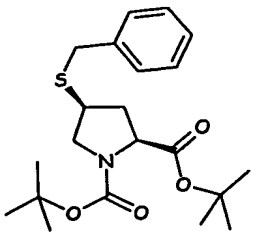
To a solution of (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (CAS Reg. No. 170850-75-6) (1g, 3.48mmol) in 20ml of CH_2Cl_2 was added pyridine (3.9ml) and *p*-toluene sulphonyl chloride (0.7g, 3.67mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 72 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (100ml) and washed with saturated citric acid solution (50ml) then water (50ml). The organic phase was dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate:heptane (3:10) to give the title compound (1.5g, 98%) as a colourless gum.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.39-1.49 (18H, m), 2.01-2.16 (1H, m), 2.33-2.6 (4H, m), 3.50-3.64 (2H, m), 4.20-4.29 (1H, m), 4.96-5.06 (1H, m); 7.31-7.40 (2H, m), 7.65-7.80 (2H, m).

LRMS (electrospray) : m/z [MH^+] 464, [MH^-] 440

Preparation 2

(2S, 4S)-4-Benzylsulfanyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



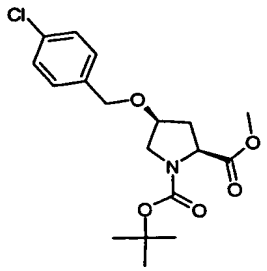
To a solution of Preparation 1 (200mg, 4.53mmol) in ethanol (10ml) under a nitrogen atmosphere was added benzyl mercaptan (0.107ml, 8.86mmol) and potassium tert-butoxide (101mg, 8.86mmol) and the mixture stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (25ml) and was washed with water (10ml). The organic phase was dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by column chromatography eluting with heptane:ethyl acetate (9:1) to give the title compound (130mg, 73%) as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.38-1.50 (18H, m), 1.80-1.90 (1H, m), 2.44-2.55 (1H, m), 3.00-3.29 (2H, m), 3.70-3.78 (2H, s), 3.84-3.95 (1H, m), 4.04-4.16 (1H, m), 7.27-7.34 (5H, m).

LRMS (electrospray) : m/z [MNa^+] 416

Preparation 3

(2S,4S)-4-(4-Chloro-benzyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



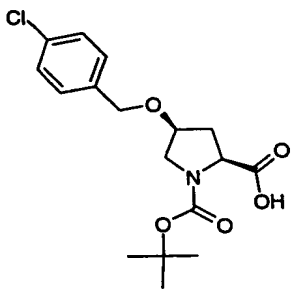
(2S, 4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyester (CAS reg 227935-38-8)(300mg, 1.0mmol) and 60% sodium hydride mineral oil dispersion (61mg, 1.1mmol) were dissolved in anhydrous dimethylformamide (9ml) at 0°C under a nitrogen atmosphere. After 10mins stirring 4-chlorobenzylbromide (265mg, 1.2mmol) in CH_2Cl_2 (1ml) was added drop wise and the reaction mixture stirred to room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (25ml), washed with water (2 x 25ml), dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified using flash chromatography eluting with a solvent gradient 4:1 heptane:ethyl acetate, yielding the title compound (170mg, 40% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.4-1.5(m, 9H), 2.0-2.45(m, 2H), 3.5-3.8(m, 5H), 4.05-4.2(s, 1H), 4.25-4.4(m, 1H), 4.4-4.55(m, 2H), 7.3(m, 4H).

LCMS (Electrospray): m/z [MNa^+] 392.

Preparation 4

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-[(4-chlorobenzyl)oxy]-2-pyrrolidinecarboxylic acid



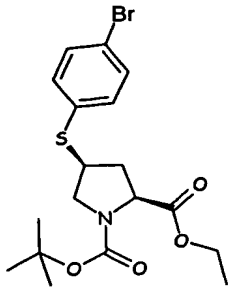
The title compound from Preparation 3 (157mg, 0.42mmol) was dissolved in tetrahydrofuran (10ml). $LiOH.H_2O$ (54mg, 1.3mmol) was dissolved in water (5ml). The two solutions were mixed, left stirring at room temperature for two days then evaporated to dryness under reduced pressure. The remaining residue was dissolved in ethyl acetate (25ml) and washed with saturated citric acid (25ml). The organic fraction was dried (magnesium sulphate), filtered and evaporated to dryness under reduced pressure. The residue was purified using flash chromatography eluting with a solvent gradient of 20:1 dichloromethane:methanol, yielding the title compound (106mg, 71% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.4(m, 9H), 2.9-3.0(m, 1H), 3.4-3.6(m, 2H), 4.2-4.7(m, 5H), 7.2-7.35(m, 4H).

LCMS (Electrospray): m/z [M^-] 354

Preparation 5

(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester



Sodium ethoxide (112mg, 1.65mmol) was added slowly to a stirred solution of 4-bromothiophenol (302mg, 1.65mmol) in EtOH (6ml) at room temperature under a

nitrogen atmosphere. A solution of (2S, 4R)-4-(toluene-4-sulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester[1] (300mg, 0.75mmol) in 1ml EtOH was added after 30 minutes and the solution was stirred for 48h. The reaction mixture was poured into 0.5M NaOH (50ml) and extracted with CH_2Cl_2 (2 x 50ml). The combined organics were dried (magnesium sulphate) and concentrated under vacuum. Flash column chromatography yielded the product as a pink solid (120mg, 40%).

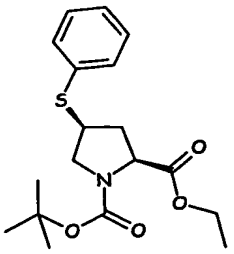
^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.25 (3H, t), 1.40 (9H, s), 2.00 (1H, s), 2.60 (1H, m), 3.35 (1H, m), 3.60 (1H, m), 3.90 (1H, s), 4.18 (2H, q), 4.22 (1H, m), 7.35 (2H, d), 7.40 (2H, d).

LRMS (Electrospray) : m/z [MNa^+] 454.

Ref: [1]CAS reg 88043-21-4 .

Preparation 6

(2S, 4S)-4-(phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester



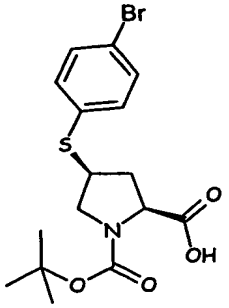
The title compound was made by the method of Preparation 5 in 40% yield as a pink solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.23 (3H, t), 1.41 (9H, s), 2.00 (1H, m), 2.61 (1H, m), 3.38 (1H, m), 3.62 (1H, m), 3.90-4.03 (1H, m), 4.15-4.35 (3H, m), 7.20-7.50 (5H, m).

LRMS (Electrospray) : m/z [MNa^+] 374.

Preparation 7

(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



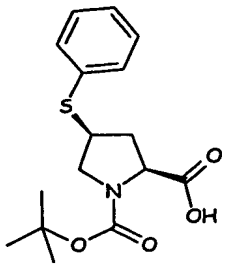
(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (Preparation 5, 120mg, 0.30mmol) was dissolved in MeOH (6ml) and 2M sodium hydroxide was added (0.83ml, 1.66mmol). The solution was stirred for 14h, concentrated and added to 0.5M HCl (50ml). The aqueous was extracted with CH_2Cl_2 (50ml) which was dried (magnesium sulphate) and concentrated. Flash column chromatography (eluting first with CH_2Cl_2 and then with 95% CH_2Cl_2 / MeOH) gave the acid as a clear liquid (130mg, 48%).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.43 (9H, s), 2.4-2.8 (2H, m), 3.35 (1H, m), 3.62 (1H, m), 3.8-4.0 (1H, m), 4.3-4.4 (1H, m), 7.28 (2H, m), 7.41 (2H, m).

LRMS (Electrospray) : m/z [M^-] 400, 402.

Preparation 8

(2S, 4S)-4-(Phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



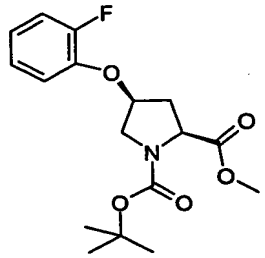
The title compound was made by the method of Preparation 7 from the title compound of Preparation 6 in 83% yield as a clear oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.41 (9H, s), 2.10 (0.5H, m), 2.38 (0.5H, m), 2.50-2.75 (1H, m), 3.36 (1H, m), 3.62 (1H, m), 3.82-4.03 (1H, m), 4.25-4.41 (1H, m), 7.20-7.45 (5H, m).

LRMS (Electrospray) : m/z [M^-] 322.

Preparation 9

4-(2-Fluoro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



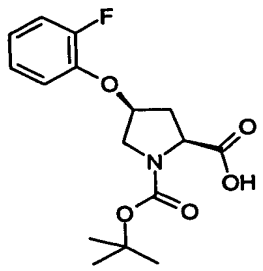
(2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No.74844-91-0) (300mg, 1.22mmol) was dissolved in THF (10 ml), and triphenylphosphine (385mg, 1.47mmol) and 2-fluorophenol (164.5mg, 1.47mmol) were added. The reaction was cooled in ice, DIAD (0.23ml, 1.2mmol) added dropwise and the reaction stirred at room temperature overnight. The mixture was concentrated in vacuo, CH_2Cl_2 (20ml) added and the solution washed with 2N NaOH (10ml). The phases were separated and the organic phase washed with saturated brine (10ml), dried over $MgSO_4$ and evaporated. The residue was dissolved in a minimum of diethylether and pentane added until solution just maintained. After seeding with triphenylphosphine oxide, the solution was cooled in ice and the resultant precipitate filtered. The filtrate was evaporated and the residue purified by flash chromatography on silica (50g) eluting initially with pentane:diethylether (2:1 by volume), then pentane:diethylether (1:1 by volume) to give the title product (388mg, 58%) as an impure oil containing diisopropylbicarbamate as an impurity.

^{1}H-NMR (400 MHz , $CDCl_3$): δ = 1.45 (d,9H), 2.35 – 2.57 (m, 2H),3.65 –3.79 (m, 5H), 4.43 – 4.57 (m, 1H), 4.88 – 5.02 (m, 1H), 6.81 – 6.98 (m, 2H), 6.98 – 7.10 (m, 2H).

LRMS (Electrospray): m/z [MNa^+] 362

Preparation 10

(2S, 4S)-4-(2-Fluoro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



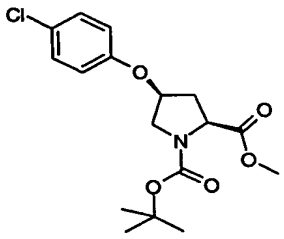
The ester (400mg, 1.18mmol) from Preparation 9 was dissolved in THF (4 ml) and $LiOH.H_2O$ (106mg, 3.53mmol) in water (2ml) was added. The mixture was stirred at room temperature overnight. After washing with CH_2Cl_2 (10ml), the aqueous solution was adjusted to pH 2 with saturated aqueous citric acid and re-extracted with CH_2Cl_2 (2 x 10ml). The combined organic extracts were backwashed with saturated brine, dried over $MgSO_4$, filtered and evaporated to give the title compound as a white solid (383mg, 49%) containing a small impurity of diisopropylbicarbamate (2%) by NMR.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.16-1.70 (m, 9H), 2.20-2.92 (m, 2H), 3.58-3.85 (m, 2H), 4.38-4.63 (m, 1H), 4.83-5.02 (m, 1H), 6.78-7.17 (m, 4H).

LRMS (Electrospray) : m/z [M-1] 324

Preparation 11

(2S, 4S)-4-(4-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



(2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 74844-91-0) (1.10g, 4.08mmol) was dissolved in THF (25ml) and 4-chlorophenol (0.78g, 6.12mmol) and triphenylphosphine (1.6g, 6.12mmol) were added. The solution was cooled in and ice bath and DIAD (0.96ml, 4.88mmol) added

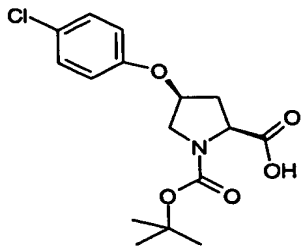
dropwise. The reaction was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in diethylether (20ml) and pentane added until solution was only just maintained. The solution was seeded with tiriphenylphosphine oxide and cooled in ice. The resultant precipitate was filtered and the filtrate evaporated. The residue was purified by flash chromatography on silica (100g), loading with pentane : diethylether (2:1 by volume) and eluting with pentane : diethylether (1 : 1 by volume) to give the title compound as a colourless oil (1.35g, 69%) containing a small impurity of diisopropylbicarbamate (CAS Reg. No.19740-72-8) by NMR.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.43 (d, 9H), 2.36-2.57 (m, 2H), 3.61-3.81 (m, 5H), 4.39-4.59 (m, 1H), 4.80-4.90 (m, 1H), 6.64-6.78 (m, 2H), 7.18-7.30 (m, 2H).

LRMS (Electrospray): m/z [MNa^+] 378

Preparation 12

(2S, 4S)-4-(4-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



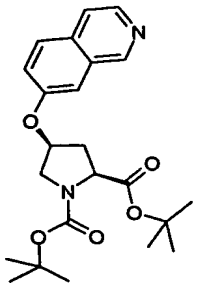
The ester from Preparation 11 was dissolved in THF (30ml) and a solution of $LiOH.H_2O$ (440mg, 10.56mmol) in water (15ml) was added. The reaction was stirred at room temperature overnight, and then the solvent concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20ml) and saturated aqueous citric acid solution (10ml) and the phases separated. The organic layer was washed with saturated brine (10ml), dried over $MgSO_4$, and evaporated. The crude product was partially purified by flash chromatography on silica (100g) eluting initially with CH_2Cl_2 and then CH_2Cl_2 : MeOH (25 : 1 by volume) to give material which still contained diisopropylbicarbamate by NMR. Recrystallisation from EtOAc yielded white crystals which were filtered and washed with EtOAc: pentane (1 :1) to give the title compound (517mg, 55%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23-1.67 (m, 9H), 2.20-2.88 (m, 2H), 3.55-3.81 (m, 2H), 4,40-4.61 (m, 1H), 4.78-4.92 (m, 1H), 6.63-6.84 (m, 2H), 7.11-7.32 (m, 2H)

LRMS (Electrospray) : m/z [M-1] 340

Preparation 13

(2S, 4S)-4-(Isoquinolin-7-yloxy)-pyrrolidine-1,2-dicarboxylicacid di-tert-butyl ester



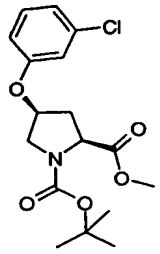
The title compound was synthesised from (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (CAS Reg. No. 170850-75-6) and isoquinolin-7-ol using the same method as preparation 11 and gave the title compound as an oil in 15% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41-1.53 (m, 18H), 2.43-2.63 (m, 2H), 3.68-3.97 (m, 2H), 4.30-4.52 (m, 1H), 4.99-5.06 (m, 1H), 7.08 -7.16 (m, 1H), 7.41-7.77 (m,, 3H), 8.42 (d, 1H), 9.10-9.18 (m, 1H).

LC/MS (Electrospray): m/z [MH^+] 415

Preparation 14

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



To a stirred solution of (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 74844-91-0) (0.3g, 1.22mmol), 3-chlorophenol (0.189g, 1.47mmol) and triphenylphosphine (0.385g, 1.47mmol) in THF (2ml) cooled at

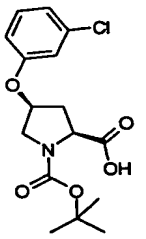
0ºC under N_2 was added dropwise the diisopropylazodicarboxylate (0.29ml, 1.47mmol). The mixture was stirred for 3 days at room temperature. The solvent was removed in vacuo and the product was purified by chromatography on silica gel using ether/n-pentane: 40/60 as eluent to afford 0.27g (62%) of a mixture of the title compound and reduced diisopropyl azodicarboxylate (1/1) as an oil.

1H NMR (400MHz, $CDCl_3$): δ = 1.46, 1.49 (2 x s, 9H), 2.47 (2H, m), 3.71 (5H, m), 4.42 (1H, m), 4.42, 4.54 (1H, 2 x m), 4.87 (1H, m), 6.68 (1H, m), 6.79 (1H, s), 6.92 (1H, m), 7.18 (1H, m).

LRMS (Electrospray): m/z 378 (MNa^+).

Preparation 15

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



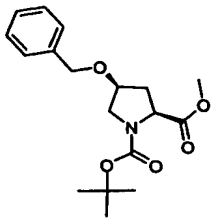
To the products from Preparation 14 (0.25g, 0.7mmol) in THF (4ml) was added a solution of lithium hydroxide (50mg) in water (4ml). The mixture was stirred overnight then water (10ml) and ether (20ml) were added. The aqueous phase was washed twice with ether (2x20ml) then acidified with 2N HCl and extracted with ether (2x20ml). The ethereal phases were dried (magnesium sulphate), filtered and evaporated to yield the title compound (80mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42, 1.48 (2 x s, 9H), 2.30-2.70 (m, 2H), 3.60-3.80 (m, 2H), 4.40-4.60 (m, 1H), 4.86 (m, 1H), 6.71 (m, 1H), 6.82 (m, 1H), 6.94 (m, 1H), 7.16 (m, 1H).

LRMS (Electrospray): m/z [MNa^+] 364, 340 [M-1] 340.

Preparation 16

(2S,4S)-4-Benzyloxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



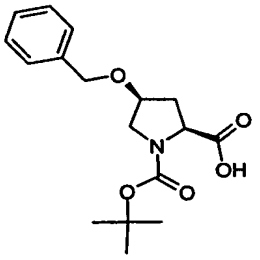
(2S, 4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyester (CAS reg 227935-38-8)(300mg, 1.2mmol) and 60% sodium hydride mineral oil dispersion (61mg, 1.5mmol) were dissolved in anhydrous dimethylformamide (9ml) at 0°C under a nitrogen atmosphere. After 10mins stirring benzylbromide (0.153ml, 1.3mmol) in CH_2Cl_2 (1ml) was added drop wise and the reaction mixture stirred to room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (25ml), washed with water (2 x 25ml), dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified using flash chromatography eluting with a solvent gradient 4:1 heptane:ethyl acetate, yielding the title compound (167mg, 42% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.2-1.6(m, 12H), 2.2-2.45(m, 1H), 3.4-3.8 (m, 4H), 4.05-4.2 (m, 1H), 4.3-4.5 (m, 2H), 7.15-7.4 (m, 5H).

LCMS (Electrospray): m/z [MNa^+] 358.

Preparation 17

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(benzyloxy)-2-pyrrolidinecarboxylic acid



The title compound from Preparation 16 (167mg, 0.5mmol) was dissolved in tetrahydrofuran (10ml). $LiOH.H_2O$ (63mg, 1.5mmol) was dissolved in water (5ml). The two solutions were mixed, left stirring at room temperature for two days then evaporated to dryness under reduced pressure. The remaining residue was dissolved in ethyl acetate (25ml) and washed with saturated citric acid (25ml). The organic fraction was dried (magnesium sulphate), filtered and evaporated to dryness under reduced

pressure. The crude compound (150mg, 94% yield) was taken on to the next stage (Example 9) as an oil.

LCMS (Electrospray): m/z [M^-] 320, [MNa^+] 344.

Pharmaceutical Composition Examples

In the following Examples, the term 'active compound' or 'active ingredient' refers to a compound of formula (I) or a pharmaceutically acceptable salt, solvate or pro-drug thereof, according to the present invention.

(i) Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

	mg/tablet	mg/tablet
(a) Active ingredient	250	250
(b) Lactose B.P.	210	26
(c) Sodium Starch Glycollate	20	12
(d) Povidone B.P.	15	9
(e) Magnesium Stearate	5	3
	500	300

Composition B

	mg/tablet	mg/tablet
(a) Active ingredient	250	250
(b) Lactose 150	150	-
(c) Avicel PH 101	60	26
(d) Sodium Starch Glycollate	20	12

(e) Povidone B.P.	15	9
(f) Magnesium Stearate	5	3
	500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in formulation E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

Composition F (Controlled release composition)

	mg/tablet
(a) Active ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.C.	28
(e) Magnesium Stearate	7
	700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudgragit L). Except

for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

	mg/capsule
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2
	420

Composition C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 BP	350
	600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

	mg/capsule
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	13
	513

The controlled release capsule formulation can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

	mg/capsule
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Cellulose Acetate Phthalate	50
(e) Diethyl Phthalat	5
	555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) or a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient	0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to	10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40^{o}C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g

Glycofurol 75	1.45 g
Water for Injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient	0.25g
Sorbitol Solution	1.50g
Glycerol	1.00g
Sodium Benzoate	0.005g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is

added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250lm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (63lm)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

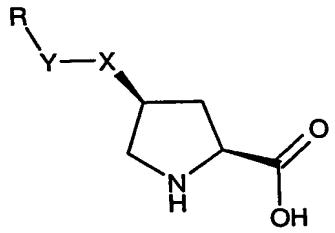
The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of $10cm^2$.

Compounds of the present invention show biological activity in the assay described hereinbefore, as illustrated by the following table:

Example No.	IC_{50} (nM)
2	119
4	72
7	210
8	5

Claims

1. Use of a compound of formula (I):



(I)

wherein

either X is O, S, NH or CH_2 and Y is CH_2 or a direct bond, or Y is O, S or NH and X is CH_2; and

R is a 3-12 membered cycloalkyl, 4-12 membered heterocycloalkyl, aryl or heteroaryl, where any ring may be optionally substituted with one or more substituents independently selected from

halogen, hydroxy, cyano, nitro, amino, hydroxycarbonyl,

C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl,

C_1-C_6 alkoxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, perfluoro C_1-C_6 alkyl, perfluoroC_1-C_6 alkoxy,

C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, di-C_1-C_6 alkylaminoC_1-C_6 alkyl,

C_1-C_6acyl, C_1-C_6acyloxy, C_1-C_6acyloxyC_1-C_6 alkyl, C_1-C_6 acylamino,

C_1-C_6 alkylthio, C_1-C_6 alkylthiocarbonyl, C_1-C_6 alkylthioxo, C_1-C_6 alkoxycarbonyl,

C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino,

aminosulfonyl, C_1-C_6 alkylaminosulfonyl, di-C_1-C_6 alkylaminosulfonyl,

3-8 membered cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and monocyclic heteroaryl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof, in medical therapy.

2. Use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the manufacture of a medicament for the treatment of the treatment of a disorder selected from epilepsy, faintness attacks, hypokinesia, cranial

disorders, neurodegenerative disorders, depression, anxiety, panic, pain, irritable bowel syndrome, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

3. A method of treatment of a mammal, including human, of a disorder as described in claim 2, comprising effective administration of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

4. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, excluding the compounds described in Table 1.

5. A compound of formula (I) according to uses of claim 1 or 2, the method of claim 3 or claim 4, wherein X is O, S or CH_2 and Y is CH_2 or a direct bond.

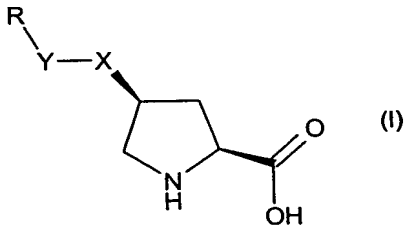
6. A compound according to claim 5 wherein R is phenyl.

7. A compound according to claim 5 or 6 wherein optional substitution on R is by halogen.

ABSTRACT

THERAPEUTIC PROLINE DERIVATIVES

The compounds of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, are proline derivatives useful in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, arthritis, neuropathalogical disorders, sleep disorders, visceral pain disorders and gastrointestinal disorders. Processes for the preparation of the final products and intermediates useful in the process are included. Pharmaceutical compositions containing one or more of the compounds are also included.



(I)

wherein

either X is O, S, NH or CH_2 and Y is CH_2 or a direct bond, or Y is O, S or NH and X is CH_2; and

R is a 3-12 membered cycloalkyl, 4-12 membered heterocycloalkyl, aryl or heteroaryl, where any ring may be optionally substituted with one or more substituents independently selected from

halogen, hydroxy, cyano, nitro, amino, hydroxycarbonyl,

C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl,

C_1-C_6 alkoxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, perfluoro C_1-C_6 alkyl, perfluoroC_1-C_6 alkoxy,

C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, di-C_1-C_6 alkylaminoC_1-C_6 alkyl,

C_1-C_6acyl, C_1-C_6acyloxy, C_1-C_6acyloxyC_1-C_6 alkyl, C_1-C_6 acylamino,

C_1-C_6 alkylthio, C_1-C_6 alkylthiocarbonyl, C_1-C_6 alkylthioxo, C_1-C_6 alkoxycarbonyl,

C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino,

aminosulfonyl, C_1-C_6 alkylaminosulfonyl, di-C_1-C_6 alkylaminosulfonyl, 3-8 membered cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and monocyclic heteroaryl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.